Review Article

Obstetric Medicine

Obstetric Medicine
2015, Vol. 8(3) 126–132
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DOI: 10.1177/1753495X15589223
obm.sagepub.com
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Acute respiratory failure in pregnancy

Stephen E Lapinsky

Abstract

Respiratory failure affects up to 0.2% of pregnancies, more commonly in the postpartum period. Altered maternal respiratory physiology affects the assessment and management of these patients. Respiratory failure may result from pregnancy-specific conditions such as preeclampsia, amniotic fluid embolism or peripartum cardiomyopathy. Pregnancy may increase the risk or severity of other conditions, including thromboembolism, asthma, viral pneumonitis, and gastric acid aspiration. Management during pregnancy is similar to the nonpregnant patient. Endotracheal intubation in pregnancy carries an increased risk, due to airway edema and rapid oxygen desaturation following apnea. Few data are available to direct prolonged mechanical ventilation in pregnancy. Chest wall compliance is reduced, perhaps permitting slightly higher airway pressures. Optimizing oxygenation is important, but data on the use of permissive hypercapnia are limited. Delivery of the fetus does not always improve maternal respiratory function, but should be considered if benefit to the fetus is anticipated.

Keywords

Pregnancy, obstetric, respiratory failure, mechanical ventilation

Inadequate gas exchange due to pulmonary or extra-pulmonary conditions may produce hypoxemic (type 1) or hypercapnic (type 2) respiratory failure. Respiratory failure may complicate about 0.1% to 0.2% of pregnancies. The pregnant patient is at risk of various pregnancy-specific conditions as well as other diseases, which may precipitate respiratory failure (Table 1). Maternal hypoxemia and hypercapnia carry potential risks for the fetus. This review discusses the causes, risks, and management of respiratory failure in pregnancy.

Respiratory physiologic changes in pregnancy

Hormonal changes in pregnancy affect the upper respiratory tract and cause airway hyperemia and edema.[1] The diaphragm is displaced upwards by up to 4 cm, but the potential loss of lung volume is offset by widening of the anteroposterior and transverse thoracic diameters. Functional residual capacity (FRC) decreases by 10% to 25% by term.[2] The vital capacity remains unchanged, and total lung capacity decreases only minimally. Measurements of airflow (FEV1) and lung compliance are not altered during pregnancy, but chest wall and total respiratory compliance are reduced in the third trimester.[3]

Minute ventilation increases progressively during pregnancy, beginning in the first trimester and reaching 20% to 40% above baseline by term. An increase in respiratory drive is caused by elevated serum progesterone levels, producing an increase in tidal volume with very little change in respiratory rate.[4] A respiratory alkalosis develops with compensatory renal excretion of bicarbonate, with $PaCO_2$ falling to 28 to 32 mmHg (3.8–4.3 kPa) and plasma bicarbonate falling to 18 to 21 mEq/L.[5] Alveolar-to-arterial oxygen tension differences (P_AO_2-P_aO_2) are usually unchanged by pregnancy, although mild hypoxemia may develop in the supine position as FRC diminishes near term. Oxygen consumption is increased, beginning in the first trimester and reaching 20% to 33% above baseline by the third trimester. The combination of a reduced FRC and increased oxygen consumption cause the pregnant patient to the rapidly develop hypoxia in response to hypoventilation or apnea.[6]

Alkalosis may worsen fetal oxygenation by reducing uterine blood flow.[7] This can occur during hyperventilation related to labor as well as due to a metabolic alkalosis that can be produced by volume depletion and vomiting. Adequate pain relief blunts this ventilatory response, and can correct the hyperventilation associated with active labor.

Causes of respiratory failure in pregnancy

Respiratory failure may be caused by several pregnancy-specific complications, as well as by other conditions, some of which may be exacerbated by pregnancy (Table 1). The more common conditions are reviewed, with a brief outline of specific management in pregnancy.

Asthma

Asthma affects 4% to 8% of the general population and is a common pulmonary disorder in pregnancy. Approximately a third of asthmatics remain unchanged during pregnancy, while a similar proportion deteriorate or improve.[8] Asthma during pregnancy is associated with adverse effects, including an increased incidence of preterm labor, low neonatal birth weight, increased perinatal mortality, and an association with preeclampsia, chronic hypertension, and complicated labor.[9,10]

Management of the acute asthmatic attack during pregnancy is not different to management in the non-pregnant patient. A large body of literature exists demonstrating the lack of teratogenicity of drugs used in the pharmacotherapy of asthma in pregnancy. In general, the risks of poorly controlled asthma far outweigh the possible adverse effects of drug therapy.[11,12] Selective short-acting beta$_2$-agonists have demonstrated an acceptable safety profile for the fetus,[13] although nonselective beta-agonists such as epinephrine carry a risk of uterine vasoconstriction and are probably best avoided for treatment of asthma. Systemic corticosteroids are indicated in similar circumstances to the nonpregnant patient; however, intrauterine growth restriction has been documented, associated with either the use of corticosteroids or with asthma severity.[14] Halogenated corticosteroids (such as prednisolone, prednisone) do not cross the placenta to a significant degree, so fetal and neonatal adrenal suppression is not a major concern with these drugs.

Mount Sinai Hospital and the Interdepartmental Division of Critical Care, University of Toronto, Toronto, Canada

Corresponding author:
Stephen Lapinsky, Mount Sinai Hospital and the Interdepartmental Division of Critical Care, University of Toronto, 600 University Ave #18-214, Toronto M5G 1X5, Canada.
Email: stephen.lapinsky@utoronto.ca

Labor and delivery carry some risks for asthmatic patients, partly due to the drugs commonly administered. Narcotics other than fentanyl may release histamine, which can worsen bronchospasm. Oxytocin is the optimal agent for labor induction and for postpartum hemorrhage, but 15-methyl prostaglandin F_2-alpha, methylergonovine, and ergonovine may cause bronchospasm and should be avoided in asthmatics if possible.

Pulmonary infections

The pregnant woman is at risk of increased susceptibility or increased severity of some infections. Changes occur in a pregnant woman's immune system to allow tolerance to paternally derived fetal antigens. Down regulation of cell-mediated immunity occurs, balanced by an intact or upregulated humoral immune response.[15,16]

Pneumonia is a significant cause of maternal and fetal morbidity and mortality.[17,18] The incidence does not appear to be higher than that in the general population. Pregnancy is associated with an increased risk of complications of pneumonia, including respiratory failure. Pneumonia may produce pregnancy complications, including preterm labor, small-for-gestational-age, and intrauterine and neonatal death.[17–19] Bacterial pneumonia has a similar microbiologic spectrum to the usual community-acquired pneumonia in nonpregnant patients. The diagnosis of pneumonia can often be delayed because of reluctance by physicians or the patient to obtain a chest radiograph, due to inappropriate concern of radiation exposure (Table 2). Antibacterial therapy is similar to treatment in the nonpregnant patient, although drugs such as tetracyclines and quinolones should be avoided if possible.[19]

Viral pneumonia carries a risk of significant morbidity in pregnancy, with increased mortality rates compared with the general population. In influenza pandemics, the maternal mortality rate has consistently been higher than the general population. Vaccination of pregnant women is strongly recommended.[20] The 2009 influenza A (H1N1) pandemic was associated with a high incidence of severe disease in pregnant women, with significant mortality.[21] Amantadine has been used in pregnancy as treatment and as prophylaxis, and oseltamivir was used quite extensively in pregnancy in the 2009 epidemic.[22] Varicella pneumonia is also associated with significant morbidity and mortality during pregnancy. In one review, a 35% mortality rate was reported in pregnancy, compared with 10% in other adults[23] although not all prospective studies have confirmed this increased risk in pregnancy. Treatment with acyclovir is necessary and reduces mortality in gravid patients.[24]

Although fungal pneumonias are uncommon in pregnancy, coccidioidomycosis is more likely to disseminate in pregnancy.[25] This occurs particularly in the third trimester and has been attributed to subtle impairment of cell-mediated immunity and to a stimulatory effect of progesterone and 17-beta-estradiols on fungal proliferation.[26] Amphotericin is the accepted therapy for disseminated coccidioidomycosis.

Table 1. Causes of acute respiratory failure in the obstetric patient.

Specific to pregnancy	Pulmonary edema due to preeclampsia ARDS due to chorioamnionitis ARDS related to placental abruption Peripartum cardiomyopathy Amniotic fluid embolism Tocolytic-associated pulmonary edema Trophoblastic embolism
Risk increased by pregnancy	Venous thromboembolism Gastric acid aspiration Transfusion related acute lung injury Asthma ARDS due to sepsis, often pyelonephritis Pneumonia (e.g. varicella, fungal) Stenotic valvular heart disease, pulmonary hypertension
Nonspecific conditions	Trauma Drugs/toxins Pancreatitis

Pulmonary edema

Due to the cardiac physiological changes of pregnancy, women with pre-existing heart disease are at risk of cardiac decompensation. Those with cyanotic disease, left heart valvular stenotic lesions, or systolic dysfunction are at most risk[27] with pulmonary edema occurring during pregnancy or postpartum, related to large shifts in intravascular volume associated with delivery. The rise in cardiac output and heart rate that occur during gestation increase the gradient across a stenotic mitral valve.[28] In contrast, the reduced systemic vascular resistance (SVR) of pregnancy mitigates the effects of mitral and aortic regurgitation and of the left-to-right intracardiac shunts, but worsens the effects of Eisenmenger's syndrome and uncorrected tetralogy of Fallot. Changes in SVR and cardiac output induced by pregnancy can alter fractional shunts producing hypoxemia, and precipitating pulmonary edema. Specific to pregnancy is the condition of peripartum cardiomyopathy, a disorder that occurs in 1 of 1300 to 15,000 deliveries. This condition may present with congestive heart failure, and is associated with a risk of pulmonary and systemic embolization.[29]

Preeclampsia can result in pulmonary edema, which occurs in about 2.9% of patients with this condition.[30] The hemodynamic

Table 2. Risk of radiation exposure from common chest radiographic investigations.[38,42,43,82]

	Maternal breast exposure mGy	Fetal radiation exposure mGy	Fetal radiation exposure rad	Comments
Investigation				
Chest radiograph	0.2	0.010	0.001	Minimal risk to fetus
Ventilation-perfusion scan	<1.5	0.20–1.0	0.02–0.10	If perfusion normal, avoid ventilation scan
CT chest /angiogram	10–18	0.1–0.8	0.01–0.10	The larger the fetus, the greater the exposure
Adverse effect				
Increase risk of childhood leukemia		>20–50	>2–5	May be reached with abdominal-pelvic CT scan
Teratogenicity		>100–200	>10–20	Levels reached with radiation therapy
Neurological developmental abnormalities		>100	>10	Most vulnerable period 8–15 weeks gestation

findings in preeclampsia include normal or low left ventricular preload, increased afterload, with a normal or low cardiac output. Systolic and diastolic function may be impaired.[31] When pulmonary edema occurs, it usually presents in the postpartum period, related to fluid administration at delivery and return of blood from the contracting uterus to the central circulation. Other contributing effects include the low colloid oncotic pressure and abnormal vascular permeability.

Pulmonary edema may sometimes occur during the systemic administration of beta$_2$-sympathomimetic agents used to inhibit premature labor.[32] It usually presents at least 24 h after initiation of beta-adrenergic therapy, and treatment often only requires discontinuation of beta-adrenergic therapy but furosemide is usually administered. Pulmonary edema may also complicate tocolysis with calcium channel blockers.[33]

Pulmonary thromboembolic disease

Although venous thromboembolism is not common in pregnancy, occurring with an incidence of about 0.6–2 per 1000 deliveries,[34] this incidence is about five times as great as in matched nongravid controls. Pulmonary thromboembolism is a leading cause of maternal mortality,[34,35] accounting for about 10% of pregnancy-related deaths in the United States.[36] The risk for thrombosis is increased in pregnancy, because of the increase in coagulation factors (V, VIII, X, and von Willebrand factor), a fall in protein S levels,[37] uterine compression of the inferior vena cava and the left iliac vein, and local trauma to pelvic veins during delivery. The peak incidence of thromboembolism is in the postpartum period, especially after cesarean section.

The initial diagnostic test for venous thrombosis should be duplex ultrasonography if symptoms or signs of DVT are present.[38] Radiological investigations can be performed safely in pregnancy (Table 2). The diagnosis of pulmonary embolism in pregnant women can utilize ventilation-perfusion (V/Q) scanning or CT pulmonary angiography. Radiation exposure for a standard technetium-labeled macroaggregated albumin perfusion scan is about 0.18 mGy (18 mrad),[39] which can be reduced by halving the dose without significantly impairing resolution. The ventilation portion of the study can be avoided if perfusion is normal. Computed tomographic (CT) angiography is associated with similarly low radiation doses to the fetus.[40,41] In addition to the potential fetal risks of radiation exposure, significant maternal breast radiation exposure may occur particularly with CT scans (Table 2). Breast tissue of women under 40 years has relatively high radiosensitivity and the proliferative pregnant breast tissue may be more susceptible to radiation exposure, although limited evidence exists to support this concern.[42,43] V/Q scanning in pregnancy is usually associated with high-quality scans, due to the patients' younger age and lack of co-morbidity, while CT-angiography may be technically suboptimal, due to the increased cardiac output in pregnancy. Noncontrast magnetic resonance imaging can image pelvic and lower extremity veins, gadolinium being preferably avoided in pregnancy.[38]

Low molecular weight heparin (LMWH) is safe in pregnancy and is associated with fewer adverse effects than unfractionated heparin.[44] A weight-adjusted dosing regimen should be used,[45] and some authors suggest titrating the dose to achieve anti-factor Xa levels of 0.5 to 1.2 U/mL 3 to 6 h after injection.[34] Treatment is usually given for at least 6 weeks postpartum (a minimum duration of 3 months). LMWH should be held 24 h prior to delivery or neuraxial anesthesia (for twice daily dosing). Warfarin is usually avoided in pregnancy for this indication as it crosses the placenta and causes nasal, ophthalmologic, and central nervous system abnormalities. Temporary, retrievable IVC filters may be placed during pregnancy with limited fetal radiation exposure, the major concern being extrinsic compression of the IVC by the uterus. Thrombolytic therapy has been used successfully in life-threatening thromboembolism during pregnancy, with a complication rate similar to that in nonpregnant women.[46]

Amniotic fluid embolism

The syndrome of amniotic fluid embolism occurs in about 7.7 per 100,000 pregnancies.[47] This most often occurs related to labor and delivery or after uterine manipulation, and is characterized by development of severe dyspnea and hypoxemia, followed by seizures and cardiovascular collapse or arrest. Those who survive the initial event may develop disseminated intravascular coagulation and ARDS.[48] Risk factors for amniotic fluid embolism include older maternal age, high parity, cesarean section, low uterine segment laceration, and meconium staining of amniotic fluid. The mechanism of amniotic fluid embolism involves traumatic opening of uterine vessels, as suggested by data from a U.S. registry of cases, where 78% of the patients had ruptured membranes and several had just undergone intrauterine procedures.[49] Fetal squamous cells are found in the maternal pulmonary circulation at autopsy, but this finding is not specific for the syndrome as fetal cells may be recovered from pulmonary artery catheters in symptom-free patients with other diagnoses.[50] Hemodynamically, the mechanism involves the acute development of pulmonary hypertension followed by left ventricular dysfunction.[51] These effects may be caused by constituents of amniotic fluid, including leukotrienes and arachidonic acid metabolites. In view of some similarities to anaphylaxis it has been suggested that the disorder be renamed *anaphylactoid syndrome of pregnancy*.[49] Recent evidence suggests a possible pathogenic and prognostic role for low C1 esterase inhibitor levels.[52] Radiographically, the patients usually develop bilateral pulmonary infiltrates.

There is no treatment specific for amniotic fluid embolism, and management consists of supportive care for the associated disseminated intravascular coagulation and left ventricular and respiratory failure. If the fetus survives the initial event, it should be promptly delivered. In cases of imminent maternal demise, emergency postmortem or periresuscitative cesarean section should be performed, as in other instances of cardiopulmonary resuscitation in pregnancy.[53] The maternal mortality rate has been reported as high as 86% but in more recent reports, as low as 22%.[47] Amniotic fluid embolism may account for 14% of all maternal deaths.[49]

Acute respiratory distress syndrome

The pregnant patient is at risk of developing acute lung injury from pregnancy-associated complications as well as other conditions.[54] Acute respiratory distress syndrome (ARDS) in not uncommon in pregnancy and is a leading cause of maternal death (Table 1).[55] The pregnant state may predispose to the development ARDS by a number of mechanisms, including the increased circulating blood volume, the reduced serum albumin level,[54] a possible upregulation of components of the acute inflammatory response[56] and increased capillary leak.

There are few differences in the management of the pregnant patient who has ARDS compared with one who is not pregnant. Survival from ARDS appears to be as good as or better than that in the general population, likely because of these patients' young age, lack of comorbidity, and the reversibility of many of the predisposing conditions, with an anticipated 40% to 75% survival rate.[57]

Gastric acid aspiration is an important cause of maternal acute lung injury. The increased risk in pregnancy is related to the increased intra-abdominal pressure caused by the enlarged uterus, the effect of progesterone lowering the tone of the esophageal sphincter, as well as use of the supine position for delivery. About two thirds of cases of aspiration occur in the delivery suite. All pregnant patients should be considered to have a full stomach. Aspiration of gastric contents with pH 2.5 or lower causes chemical pneumonitis with permeability edema.

Transfusion related acute lung injury (TRALI) is a complication of blood component therapy, which may occur in pregnancy.[58] The clinical presentation is of sudden onset of dyspnea during, or within 6 h, of transfusion of plasma-containing blood products. The clinical picture is indistinguishable from ARDS from other causes, and the differential diagnosis includes circulatory fluid overload. Management is supportive and most patients improve within a few days, although fatal outcomes may occur.

Restrictive lung disease

Interstitial lung diseases (ILD) are not very common in woman in their childbearing years, as most diseases affect an older demographic. There are conditions which may occur in this age-group and some, including lymphangioleiomyomatosis and systemic lupus erythematosus, may worsen as a result of pregnancy. Physiologically, a concern in the woman with ILD in pregnancy is hypoxemia and difficulty in meeting the increased oxygen requirements of pregnancy. The increased cardiac output of pregnancy (and therefore shortened alveolar capillary transit time) in the face of a diffusion defect, predisposes to hypoxemia.

Women with chest wall restrictive disease (e.g. kyphoscoliosis) or neuromuscular weakness may not be able to meet the increased ventilation requirements of pregnancy, putting them at risk of respiratory failure. Due to the lack of pulmonary parenchymal disease, oxygenation problems are less of a concern.

Marked obesity may also reduce lung volumes, potentially impacting on pregnancy. Some physiological effects of pregnancy (e.g. upper airway edema) may predispose to the development of obstructive sleep apnea (OSA), while other physiological effects (e.g. respiratory stimulation by progesterone) may be protective.[59] Obstructive sleep apnea during pregnancy may be associated with gestational hypertensive disorders, gestational diabetes, and fetal growth restriction.[59]

Few data exist on the management and outcome in patients with restrictive lung disease, but it appears reasonably well tolerated in pregnancy.[60,51] Small case series have described successful pregnancy outcome in women with vital capacities less than 40% predicted.[60–62] Successful pregnancy in such patients requires an experienced, multidisciplinary team approach. Assessment may require pulmonary function testing, arterial blood gases and echocardiography. Nocturnal hypercapnia may precede daytime ventilatory failure in patients with neuromuscular disease, and a sleep study with CO_2 monitoring may be of value to identify patients at risk.[61] If associated pulmonary hypertension exists in these patients, this increases maternal risk significantly. Noninvasive ventilation has been used to support respiratory function through the latter part of pregnancy and during labour.[62] In all these patient groups, additional intercurrent illness such as pneumonia or influenza could result in significant respiratory compromise.

Cystic fibrosis

With improved treatment of cystic fibrosis (CF), median survival has increased and pregnancy is not uncommon, despite the frequent infertility of women with this condition. Pregnancy in CF patients has been associated with adverse fetal and maternal outcomes.[63] From a fetal perspective, preterm labor and perinatal death rate are increased. Pregnancy has little effect on patients with stable CF, although poor outcomes have been seen in those with severe disease.[64] An FEV1 below 60% of predicted and the presence of pulmonary hypertension are poor prognostic factors for both mother and infant.

Ventilatory management in the pregnant patient

Intubation

Endotracheal intubation in the pregnant patient carries considerable risk. Failed intubation is 8 times more common in the obstetric population than in other anesthetic intubations.[65] The reduced FRC and increased oxygen consumption in pregnancy cause rapid oxygen desaturation during apnea or hypoventilation.[6] Upper airway mucosal edema and friability can adversely affect visualisation and increase the risk of bleeding. Nasal intubation should be avoided and a smaller size endotracheal tube may be required. Preoxygenation is important, but overventilation and respiratory alkalosis must be avoided. The risk of aspiration should always be considered.

Noninvasive ventilation

Noninvasive ventilation is well suited to short-term ventilatory support, and avoids the potential complications of endotracheal intubation and the associated sedation. This modality has a role in obstetric respiratory complications which reverse rapidly.[66] The major concern with this form of ventilator support is the risk of aspiration. Noninvasive ventilation should therefore only be used in the pregnant patient who is alert, protecting her airway and where there is an expectation of a relatively brief need for mechanical ventilation.

Invasive mechanical ventilation

Prolonged mechanical ventilation of pregnant patients in the ICU is relatively uncommon, and few data are available to guide management. Hyperventilation and alkalosis should be avoided to prevent uterine vasoconstriction.[67] Lung protective ventilation, sometimes producing permissive hypercapnia, has not been assessed in pregnancy. Chest wall compliance is reduced by the enlarging uterus, and the usual pressure limits (e.g. plateau pressure of 35 cmH_2O) may not be appropriate. Slightly higher airway pressures (without increased transpulmonary pressure) may be needed to achieve appropriate tidal volumes in pregnant women near term.

Blood gas abnormalities may adversely affect the fetus.[68] Oxygenation should be optimized to ensure adequate fetal oxygenation. A maternal oxygenation goal of pO_2 greater than 70 mmHg has been suggested.[69,70] However, a short-term study of controlled maternal hypoxemia (<85%) using inhalation of 10% oxygen demonstrated no adverse effects on fetal monitoring.[71] Maternal oxygen saturation is only one factor contributing to fetal oxygenation, placental perfusion usually playing a more significant role.

While excessive hypocapnia may cause fetal harm by reducing placental perfusion,[72] the effects of hypercapnia on the fetus are less clear. Maternal CO_2 levels are normally reduced to about 27 to 34 mmHg, producing a gradient to facilitate placental excretion of fetal CO_2. Permissive hypercapnia has not been evaluated in pregnancy, and maternal hypercapnia could produce fetal respiratory acidosis. This acidosis likely does not have the same ominous implications for the fetus as the lactic acidosis produced by hypoxemia, which implies significant tissue hypoxemia.[73] Small clinical studies have evaluated the short-term effect of mild hypercapnia in pregnancy. Women undergoing cesarean delivery were subjected to mild hypocapnia (mean 23 mmHg) or mild hypercapnia (39.3 mmHg).[74] Hypocapnia produced a lower Apgar score and delayed neonatal breathing. Another small study compared ventilated women delivered with mild hypercapnia (mean CO_2 57.6 mmHg) with ventilated women with mild hypocapnia (mean CO_2 26.4 mmHg) and women managed with a local anesthesia block (mean CO_2 30.1 mmHg).[75] The hypercapnic group had a statistically significantly higher Apgar score at delivery. If necessary, mild hypercapnia with $PaCO_2$ maintained less than 60 mmHg, has been recommended for pregnancy.[76] It should be noted that the right shift of the haemoglobin oxygen dissociation curve caused by acidosis may negate the beneficial oxygen-carrying characteristics of fetal haemoglobin.

Nonconventional support

Few data are available to support the use of interventions such as inhaled nitric oxide, prone positioning and high-frequency oscillation in pregnancy, although these modalities have been used successfully and described in case reports and small series. The 2009 H1N1 influenza epidemic resulted in a marked increased utilization of extracorporeal life-support for ARDS, including pregnant patients with reasonably good outcome.[77]

Delivery of the fetus

It has been suggested that delivery of the pregnant patient with respiratory failure will result in improvement in the mother's condition.[78] However, a significant benefit to the mother has not been consistently demonstrated.[79,80] If the fetus is at a viable gestation and is at risk due to intractable maternal hypoxia, there may well be a benefit to the fetus in delivery. The mode of delivery should be determined by standard obstetrical principles. Although cesarean section may allow more rapid delivery in the critically ill patient, there is significantly increased physiological stress, and operative delivery has been associated with higher mortality in these patients.[81] Delivery should not be performed solely in an attempt to improve maternal oxygenation or ventilation. It is essential that the ICU have prearranged plans for urgent delivery and neonatal resuscitation in the event of spontaneous labor or sudden maternal or fetal deterioration. This should include immediate availability of all necessary equipment, drugs and staff contact details.

Conclusion

Respiratory failure complicates a relatively small number of pregnancies, but carries significant potential risks for both mother and fetus. Causes of respiratory failure may be related to pregnancy-specific conditions or other respiratory diseases, and management requires a multidisciplinary team approach, involving obstetrics, maternal-fetal medicine, neonatology, obstetric medicine, pulmonology, and critical care. A major decision facing this multidisciplinary team is the potential benefit to the mother of delivery—this cannot always be predicted, and the decision should be based on the overall risk balance to both mother and fetus.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Guarantor

Stephen Lapinsky

Contributorship

Stephen Lapinsky is the sole contributor to this manuscript.

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